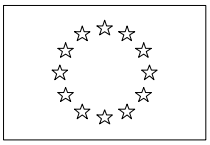

OPINION OF THE EUROPEAN GROUP ON ETHICS
IN SCIENCE AND NEW TECHNOLOGIES
TO THE EUROPEAN COMMISSION

No 17 **4th February 2003**

Original in English

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ETHICAL ASPECTS OF CLINICAL RESEARCH IN DEVELOPING COUNTRIES

Reference: Request by the European Commission on 29th May 2001
Rapporteurs: Inez de Beaufort and Yvon Englert

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The European Group on Ethics in Science and New Technologies (EGE),

Having regard to the request of Romano Prodi, President of the European Commission, to the EGE;

Having regard to the Treaty on European Union as amended by the Treaty of Amsterdam, and in particular Article 6 (formerly Article F) of the common provisions, concerning the respect for fundamental rights;

Having regard to the EC Treaty and in particular Article 152 (formerly Art. 129) on public health;

Having regard to the Charter of 28 September 2000 on Fundamental Rights of the European Union, approved by the European Council in Biarritz on October 14th 2000, in particular Article 1 on "Human dignity", Article 3 on the "Right to the integrity of the person", which refers to the principle of "free and informed consent" and Article 13 asserting freedom of research;

Having regard to the Action Plan Sciences and Society adopted by the Commission in December 2001 and Action 33 concerning the development of ethical review capacity in different regions of the world;

Having regard to the Decision 1513/2002/EC of the European Parliament and of the Council of 27th June 2002 concerning the sixth Framework Programme for Research and contributing to the creation of the European Research Area (2002-2006);

Having regard to the Council Decision of 30th September 2002 adopting a specific programme for research: "Integrating and strengthening the European Research Area" (2002-2006);

Having regard to the Directive 2001/20/EC of the European Parliament and of the Council of 4th April 2001 on good clinical practice in the conduct of clinical trials on medicinal products for human use;

Having regard to the Directive 2001/83/EC of the European Parliament and of the Council of 6th November 2001 on the Community code relating to medicinal products for human use;

Having regard to the Directive 95/46 EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and the free movement of such data;

Having regard to the Council of Europe's Convention on Human Rights and Biomedicine, signed on 4th April 1997 in Oviedo, in particular Article 15 about freedom of research and Articles 16 and17 about the protection of persons undergoing research;

Having regard to the Declaration of Helsinki of the World Medical Association, adopted in 1964 and revised in 1975, 1983, 1989, 1996 and 2000;

Having regard to the International Ethical Guidelines for biomedical research involving human subjects of the Council for International Organizations of Medical Sciences (CIOMS) adopted in 1993 and revised in October 2002;

Having regard to the guidelines related to the conduct of clinical trials published by the International Conference on Harmonisation;

Having regard to the reports and opinions expressed by national ethics instances on that issue, namely the report of the Nuffield Council on Bioethics (UK, 2002), the report of the National Bioethics Advisory Commission (USA, 2001) and the report of the National Committee on Ethics (FR, 1993);

Having regard to the Round Table organised by the Group on 1st October 2002 in Brussels with members of the European Parliament, jurists, philosophers, scientists, representatives of industries, representatives of religions, representatives of patients' associations and other groups of interest, and of international and European organisations (UNESCO, Council of Europe, EMEA, WTO, WIPO, EPO);

Having regard to the hearings of experts on 19th April 2002, 4th June 2002, 3rd September 2002, 25th October 2002 and 5th November 2002;

Having regard to the studies asked by the Group to the Institute for Prospective Technological Studies (Sevilla) on "the ethical controversy over the use of placebo in clinical trials in developing countries: impact on international research guidelines and scientific literature" and on "Industry-funded clinical trials in developing countries" by Dolores Ruiz Ibarreta;

Having heard the rapporteurs Inez de Beaufort and Yvon Englert;

1. WHEREAS :

BACKGROUND

1.1

In west European cultures, since the 19th century, clinical research has become an essential step to increase knowledge regarding human health in order to develop prevention, diagnosis and treatment of disease and handicap. The existing codifications by national laws or international texts concern mainly clinical research carried out for the development of new drugs, but the principles and conditions defined in these texts can also be applied to medical research regarding all other kinds of treatments or prevention.

1.2

Years of research are necessary before a new drug can be put on the market, with the following steps:

- the pre-clinical phase which may include in vitro studies, for instance on biochemical characteristics, on pharmacological properties and toxicity, and the animal studies, including the use of animal models, to test the potential therapeutic and toxic effects**,**

- the clinical phase involving human beings which takes place only when the previous steps have been fulfilled.

1.3

Clinical trials are an essential part of medical research to develop new treatments or new diagnostic methods.
Clinical trials phase I are performed with healthy volunteers to test the pharmacology and toxicity of a new product.
Clinical trials phase II are performed with a limited number of patients to test the potential effects of the drug on the disease.
Clinical trials phase III are performed on a larger number of patients to assess the efficacy and evaluate the appropriate dosage.
Clinical trials phase IV are performed after the product has been commercialised in order to identify potential rare adverse effects.

1.4

The evaluation of the efficiency of a new drug is based on the comparison of a group of patients receiving this new drug with a group receiving another already existing treatment. In the absence of any existing treatment, the comparison can be carried out with a placebo.
A new drug can also be developed in order to be added to a standard treatment and not to replace it. In such a case, the group of patients receiving the new drug in addition to the standard treatment is compared with a group who receives a placebo in addition to the standard treatment. Such cases illustrate that to belong to a placebo group in a clinical trial does not necessarily mean that this group does not receive any treatment.

In the case where another treatment already exists, the use of a placebo can also be a way to test more quickly and with a limited number of participants if a new drug has a specific effect to treat a disease. But such a placebo-controlled trial will not answer the question whether this new drug is more or less efficient than the other existing treatments.

1.5

The justification of clinical trials is to acquire knowledge in order to improve healthcare. Beside the benefit for healthcare related to the development of new therapies, the implementation of clinical trials has also an impact on the quality of healthcare and may stimulate transfer of technology and improve scientific and medical expertise. It has often an important impact in the financing of clinical institutions.
Clinical trials are set up also for commercial goals and can be done to promote marketing.

1.6

The European Commission has stimulated scientific cooperation with developing countries since 1983, through successive framework programmes, dealing with specific research areas such as health, agriculture and environment. Partnerships have been developed not only bi-laterally but also including a regional dimension with the creation of partnerships between developing countries, involving 123 countries from Asia, ACP[1], Latin America and the Mediterranean region.

1.7

The 6th Framework Programme proposes a new strategy, opening the possibility for developing countries to get EU funding for all the research areas defined in the Programme.
Furthermore, the European Commission proposed in August 2002 to initiate a long-term partnership between Europe and developing countries to join efforts to combat poverty-linked diseases such as AIDS, malaria and tuberculosis. The budget for this "European and Developing Countries Clinical Trials Partnership" (EDCTP) will be 600 million Euros, a third provided respectively by the European Community, the participating countries and industry.

1.8

Developing countries differ from industrialised countries regarding economic and social contexts. In developing countries, little or no infrastructure is available for the population at large, particularly concerning healthcare services.
In addition, cultural differences may also exist regarding traditions, family or community structures and moral values.

1.9

In industrialised countries, there is a rather homogeneous conception of what is good scientific method based on a logical and rational approach, while in other cultures, other medical traditions may exist, and our approach concerning scientific research may have no equivalent. Research activities include not only a scientific dimension but also a cultural one and this may have consequences especially during ethical evaluation of a clinical trial.

1.10

A clinical trial to assess the validity of new therapeutic or diagnostic products is a long and expensive process. During the last decade, a progressive shift of clinical research occurred from the public to the private sector. This implies that it also shifted investment from research on predominantly tropical and/or poverty-related diseases which are public health priorities to research on diseases and therapy with high economic return on investment. The contribution of the private sector, namely the pharmaceutical industry, has been rapidly growing compared to the contribution of the public sector. Furthermore, the implementation of clinical trials is more and more often carried out by intermediary structures such as Contract Research Organisations or Site Management Organisations.

1.11

There is also a trend to transfer clinical trials to countries where cost and constraints of regulations may be more favourable to their implementation, and where the high number of patients, and especially naïve patients, that is patients who have never received a treatment, facilitates the recruitment of patients to be involved in a clinical trial. This transfer of clinical research to developing countries concerns mainly Phase III and IV trials.

1.12

One can distinguish on the one hand clinical trials performed in developing countries because the disease addressed by the research, and the patient population who could benefit from it, are localised in these developing countries, including diseases which occur only in developing countries (like tropical diseases) or diseases which exist also in industrialised countries but which have a higher morbidity or mortality in developing countries; and on the other hand clinical trials performed in developing countries for reason of pure convenience.

1.13

Health problems specific to developing countries are very often linked to the social context and conditions of life in these countries. Poverty is in fact the main cause of "diseases". In the economic context of developing countries, clinical trials can help to define the best possible use of limited means. This cost-benefit effectiveness approach is then an essential part of the protocol, a preoccupation which is also more and more present in developed countries.

1.14

The clinical trials carried out in developing countries often contribute to developing new drugs which will be used in industrialised countries but will remain unavailable to developing countries. Clinical trials carried out to develop new drugs for exclusive use in developing countries, like treatment for tropical diseases, are comparatively rare.

[1] ACP : African, Caribbean and Pacific Region

LEGAL BACKGROUND

- **At national level**

1.15 National regulations

Many developed countries have their own comprehensive legislative and ethical background that should be taken into consideration in clinical trials. Lack of similar efforts in the host countries may jeopardise protection of the participants in clinical trials.

- **At Community level**

1.16 Directive 2001/83/EC

The Directive 2001/83/EC on the Community code relating to medicinal products for human use. The Directive refers to the Helsinki Declaration in its annex I part 4 (B) "*All clinical trials shall be carried out in accordance with the ethical principles laid down in the current revision of the Declaration of Helsinki*".

Concerning the use of placebo, the Directive specifies: "*In general clinical trials shall be done as 'controlled clinical trials' and if possible, randomised; any other design shall be justified. The control treatment of the trials vary from case to case and also will depend on ethical considerations; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather that with the effect of a placebo".*

1.17 Directive 2001/20/EC

The Directive 2001/20/EC on the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products was adopted on 4 April 2001. It has to be transposed by Member States in national law before May 2003 and implemented before May 2004.

Detailed guidelines for implementing the Directive have to be published by the Commission before May 2003. The objectives of the Directive are to define principles of protection for the subjects, to set Good Clinical Practice for testing medicinal products (including cell and gene therapies).

The Directive applies to all clinical trials (phase I to IV) carried out in the EU or third countries which intend to assess effects of medicinal products. It does not apply to "non-interventional trials" like epidemiological studies. The Directive applies to all populations of patients, but with special provisions regarding children and incapacitated adults unable to give their informed legal consent.

1.18 European Agency for the Evaluation of Medicinal Products (EMEA)

The EMEA was established in 1993 by the EU. The role of EMEA is to provide opinions on the basis of which the European Commission takes decisions regarding marketing authorisation for medicinal products.

When examining the file with the description of the clinical trial performed by the public or private institution requesting a marketing authorisation for a medical product, EMEA evaluates not only the effectiveness, safety and cost of the medical product but also the respecting of Good Clinical Practice, the granting of informed consent and of approval by ethical committees. When problems are identified, namely regarding ethical aspects, EMEA can advise the Commission to refuse the marketing authorisation or can advise the withdrawal of marketing authorisation already delivered by Member States. That is especially important for European companies doing their research in developing countries. This information is also made public. The EMEA intervention happens after the clinical trial is finalised and presented in the file and not before or during the trial.

1.19 EU competencies

The EU has no direct competence on the regulation of research at large which is a matter of national competencies. Nevertheless, the EU has competence for the marketing authorisation of medical products related to the single market. This authorisation is delivered by the Commission on the basis of reports made by the EMEA and can be refused in case of non-respect of ethical principles in the clinical trials. Furthermore, the EU has a responsibility to guarantee respect of ethical principles in any EU-funded research project, wherever it takes place.

- **At international level**

1.20 The International Conference on Harmonisation (ICH)

The ICH, initiated in 1990, is a joint initiative involving both regulators and industry from the EU, Japan and the US to discuss scientific and technical aspects of product registration. The purpose is to maintain a forum of dialogue between all parties and to make recommendations to achieve greater harmonisation.

Several guidelines are related to clinical trials and address the issue of placebo. The guideline on "the choice of control group" (E10) says: "*Whether a particular placebo-controlled trial is ethical may in some cases, depend on what is believed to have been clinically demonstrated and on the particular circumstances of the trials". "It should be emphasised that use of a placebo or no-treatment control does not imply that the patient does not get any treatment at all".*

1.21 The declaration of Helsinki of the World Medical Association

The World Medical Association (WMA) is an international organisation representing physicians. The association, created in 1947, is an independent confederation of the professional associates from about 70 countries. Individual physicians can also join the WMA as associate members.
It aims at promoting high standards of medical ethics and provides ethical guidance to physicians through Declarations and Statements.
The General Assembly of the WMA, which meets annually, is composed of representatives of national associations and the associated members. It is the decision-making body of the WMA.

The Declaration of Helsinki, adopted in 1964 by the 18th WMA General Assembly, states the ethical principles to be respected by physicians when carrying out medical research involving human subjects, or human material as identifiable human data.
The Declaration of Helsinki is not legally binding, but it has a recognised moral value and is widely accepted.
Since 1964, the Declaration has been amended several times. The last version was adopted in October 2000 in Edinburgh; namely with amendments relating to the use of placebos in clinical trials, following a huge debate on the issue.
The previous version states that the "best proven treatment" should be given to the control group, and in the absence of proven treatment, a placebo can be used.
In this 2000 version, Art 29 stipulates that "the best current treatment" should be given to the control group when testing a new method and that a placebo can be used when no proven treatment is available.
One year later, the WMA published an attempt at clarification, which can be considered as a compromise modifying Art. 29 and specifying the conditions to be fulfilled for the use of placebo controlled trials when proven treatment exists, namely:

- where a placebo is, for methodological reasons, necessary to determine the efficacy or safety of a new method,

or

- where the trial investigates a minor condition without risk of serious or irreversible harm for the patient.

1.22 Convention of the Council of Europe

The Council of Europe (CoE) is an intergovernmental organisation which aims at promoting human rights protection and democracy in Europe. The CoE field of activities includes health and education. The CoE, created in 1949, is composed today of 44 states, including the 15 member states of the European Union. The CoE drafted the Convention of human rights and fundamental freedoms in 1950, which is legally binding for the 41 members which signed and ratified it.

The "Convention for the Protection of Human Rights and Dignity of the Human Beings with regard to the application of Biology and Medicine" known as Convention on Human Rights and Biomedicine was opened for signature in April 1997 in Oviedo (Spain).

An additional "Protocol to the Convention on Human Rights and Biomedicine on Biomedical Research" is in preparation. The protocol will define the conditions to be fulfilled when human subjects are involved in a research project and address the issue of research carried out in countries not party to the Protocol.

1.23 The Council for International Organisations and Medical Sciences (CIOMS)

The Council for International Organisations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organisation established jointly by WHO and UNESCO in 1949. CIOMS represents a substantial proportion of the biomedical scientific community. Its membership in 2001 includes 48 international member organisations, representing many of the biomedical disciplines, and 18 national members mainly representing national academies of sciences and medical research councils.

The particular contribution of CIOMS in bioethics has been the issuance of international guidelines for the application of ethical principles in various key areas, namely the International Ethical Guidelines for Biomedical Research Involving Human Subjects (developed in conjunction with WHO) published in 1993. They have been very widely utilised, particularly in developing countries. They have been revised and updated and the new version was issued in October 2002.

ETHICAL BACKGROUND

Ethical aspects of partnership between industrialised and developing countries

1.24

Globalisation concerns an increasing number of human activities, namely research activities where projects involve parties not only at national or international level but also at world-wide level.
Because this globalisation occurs in a very heterogeneous world, because extreme wealth and poverty coexist, and injustice is a fact, the relationship between parties is not per se fair and rules must be defined to avoid exploitation and increasing injustice. Among the ethical issues to be considered, consensus exists on questions like the publication of results (even negative ones), or the need to address orphan diseases and poverty-linked diseases which are found only in developing countries. But other issues remain controversial namely:

- Under what conditions is the use of a placebo acceptable?
- When testing the efficiency of a new drug, should it be compared always with the best proven treatment even when this is usually not available in the country where the trial takes place, or should the best available treatment be used?
- Are there universal values and are they applicable whatever is the socio-cultural context?

1.25

The legitimacy of the objectives of a clinical trial is related to the analysis of its relevance regarding health priorities of the partners, the risk/benefit balance for individuals and communities, and the potential impact on healthcare of the host country. But the notion of community may be understood differently (community as citizens of a country, community as members of the same group within a country or spread between different countries, affected by the same disease, or the same social conditions). This may affect the definition of needs and health priority of the so-said community.

1.26

The positive impact of a clinical trial on healthcare is first of all the acquisition of new knowledge but it includes also the sharing of this new knowledge and know-how, the accessibility to new treatments and the capacity building induced by the implementation of the clinical trial. But a potential negative impact may also occur : the implementation of the clinical trial can disturb the local pre-existing healthcare system.

1.27

The participation in a clinical trial always implies a certain risk for the participants, either because they receive a new drug whose potential negative effects may still be unknown or because they receive a placebo and are then deprived of the benefit of the standard treatment and from the potential benefit of the new drug to be tested.

Ethical aspects related to cultural diversity

1.28

Different cultures may have different values. In a paternalistic or imperialistic approach, the sponsor of the research tends to impose his own values on the host country. In contrast, when the respect for local tradition leads to relativism and non-respect of values considered as fundamental in Europe, this implies a risk of double standards.

1.29

The way information is given to patients and the procedure of obtaining consent may vary according to the specific situation of the country where a clinical trial takes place, namely regarding the level of literacy, the level of scientific understanding, the organisation of the community, etc. That may influence the consent procedures regarding the involvement of persons, in particular women, in a clinical trial.

1.30

Different cultures may have different views regarding privacy and personal data. This may have consequences for the acceptability of certain aspects of research protocols, namely regarding data collection, and the data subject's right of access and right to object.

1.31

The organisation of society may also differ between different parts of the world. While European society is characterised by the increasing value of individualism in the search of happiness, but at the same time has a collective strong solidarity at national level for guaranteeing access to healthcare for all, other societies give more importance to the local community or to the family in a context of weak national solidarity in relation to access to health care.

Ethical aspects related to economic differences

1.32

In principle, the involvement in a clinical trial is a benevolent act and should not be induced by financial or other recompense, mainly to avoid exploitation. The protection of participants in clinical trials in industrialised countries has been built up over decades, according to a given socioeconomic background. The strict transposition of such a system of protection to developing countries, without considering their socioeconomic specificities, will not ensure the same level of

protection of the participants. The protocol cannot ignore the context where the clinical trial will take place and in a context of poverty and absence of healthcare, the fact of participating in a clinical trial may constitute for the patient the only opportunity to have access to healthcare.

1.33

The fact of carrying out research in a developing country implies additional responsibility of the sponsor towards the patients, but also towards the local community where the trials take place.
This responsibility does not end with the end of the clinical trial.

1.34

The objective of a clinical trial is often to compare a new treatment to an already established treatment. But this established treatment is not always available to all, and the term "available treatment" can cover very different situations, according to the standard of care.
In the best case, in industrialised countries, the best proven treatment is usually available for the patients even if expensive or requiring high technology.
In other cases, the best proven treatment is not accessible to the patients, who can get a less efficient but also less expensive alternative. In the worst situation, no treatment at all is available for the patients. In developing countries, some placebo trials were specifically built to find cheaper alternative solutions when the best proven treatment could not be available for economic reasons. This gave rise to the question of the legitimacy of these trials.
In addition, the trend may exist to use the placebo even when there is another existing treatment, because the use of a placebo in a clinical trial may be the quickest**,** cheapest and most efficient way to test the efficacy of a new drug. But then it deprives the patients in the control group of the existing proven treatment.

2. OPINION

The Group submits the following opinion:

2.1. SCOPE OF THE OPINION

The present opinion considers the ethical aspects of clinical trials carried out within the European research programmes in developing countries. This gives rise to ethical questions specifically linked to socio-economic inequalities and poverty but also to cultural diversity. It must be stressed that cultural diversity is a factor that may influence the practice of clinical trials independently from socio-economic factors. Moreover, concepts of industrialised and of developed countries are in themselves vague as there is continuity from very poor countries to countries with a standard of living close to developed ones. The EGE members would like to stress that the huge economic inequalities of our world are the cause of most of the problems raised in this Opinion.
This Opinion is aimed at providing help to the Commission in the exercise of its responsibility regarding the implementation of EU-funded research activities in countries which culturally or economically differ from the West European context. Some aspects of this Opinion may also be applicable to research involving cultural minorities or vulnerable groups within industrialised countries. It may also be relevant for the European Agency for the Evaluation of Medicinal Products.

2.2 GENERAL APPROACH

The implementation of EU research programmes in developing countries should be based on solidarity, in line with the Charter of Fundamental Rights which proclaims in its preamble that: "*The Union is founded on the indivisible and universal values of human dignity, freedom, equality and solidarity*". Therefore, research activities involving human subjects cannot exclusively be assimilated to an economic activity subject to market rules. On the contrary, in the context of solidarity, regarding health as a public good, rather than a commodity, it needs to be regulated according to fundamental principles.
The general approach chosen within this Opinion is that the fundamental ethical rules applied to clinical trials in industrialised countries are to be applicable everywhere. Even if some difficulties may arise in their implementation, a weakening of the standards would be in contradiction to the fundamental principles of human rights and dignity and their universal guarantee and protection.

The fundamental ethical principles applicable are those already recognized in former Opinions of the EGE, and more specifically:

- the principle of respect for human dignity and the principles of non-exploitation, non-discrimination and non-instrumentalisation,
- the principle of individual autonomy (entailing the giving of free and informed consent, and respect for privacy and confidentiality of personal data),
- the principle of justice and the principle of beneficence and non-maleficence, namely with regard to the improvement and protection of health,
- the principle of proportionality (including that research methods are necessary to the aims pursued and that no alternative more acceptable methods are available).

These fundamental ethical principles underlie the conditions to be fulfilled when implementing clinical research as defined in many international guidelines or conventions. These conditions concern the modalities of both the ethical and scientific evaluation of research protocols, the granting of free and informed consent, the protection of the patients involved and the sharing of the benefits of research.
These conditions are enforced by law in all EU countries. But a legal framework does not exist in every country where EU-funded research is carried out, or is not applicable because of the lack of means and capacities or appropriate governance systems.
The Opinion will be focused on the way to deal with particular aspects of research in developing countries.

SPECIFIC ISSUES RAISED BY DEVELOPING COUNTRIES

2.3 INEQUALITY

The huge gap between industrialised countries and developing countries regarding standards of living and especially access to healthcare is an example of the inequalities in our world. Even if the objectives and goals of scientific research cannot alone solve this unfair situation, research carried out in developing countries should avoid widening this gap even more; on the contrary, it should contribute to reducing it. The private or public investigators who do their research in developing countries have a moral duty to make a concrete contribution to overcome inequalities.

2.4 PARTNERSHIP

The involvement of all partners, from the funding institutions to the host countries or communities, is essential at each phase of the research activities, from the definition of the programme and of the research priorities, to the follow-up after the end of the trials.
The involvement of local scientists from the host country at the very early stage of the planning and implementation of the research activities is crucial to develop a culture of collaboration which is different from charity help. Their knowledge of local conditions and traditions is also necessary to identify local needs.

2.5 GLOBALISATION

In the context of globalisation of research, the optimal protection of the participant must be a priority no matter where a clinical trial is performed: thus, it should only be carried out in countries with a less adequate healthcare environment, if very strict justification can be given. The more evident ones would be:

- The trial aims at addressing specific health conditions of the countries, for instance tropical diseases;
- The trial aims at addressing diseases existing also in industrialised countries but with a specifically high incidence in developing countries.
- The trial aims at developing treatments having a specific interest for the country (for instance, a new treatment cheaper than those already existing);

2.6 HANDLING DISAGREEMENT

Both the values and ethical principles of the funding agencies and of the host country have to be considered. They are explicitly or implicitly reflected in regulatory texts or in specific customs. In the case of conflicting views between parties, every effort should be made to negotiate solutions but without compromising the respect of fundamental ethical principles. Human rights standards are to be respected explicitly in all these countries. If that does not succeed, then each party must have the right to veto.

2.7 FREE AND INFORMED CONSENT

The involvement of people with knowledge of the local conditions and traditions and able to defend the interest of those affected by the project is necessary to guarantee the most appropriate procedures of informing of the potential participants in a clinical trial.
According to the local situation, it may be appropriate to seek agreement on the implementation of a research project from persons representative of or invested with a certain authority within the community, or the family. However, free and informed consent always has to be given by each individual involved in a trial.

2.8 ETHICAL COMMITTEE

The scientific and ethical evaluation of the research protocol should be carried out by ethical committees from all countries involved. Host countries need to have a legal and ethical framework in order to take part in the clinical trial evaluation effectively and independently. The Group strongly supports EU initiatives to build local ethical committees in the host countries. It should be considered as a priority in terms of capacity building. When no local ethics committee exists, then the evaluation should be done by a mixed committee involving representatives from both EU Member States and host countries. It is essential that the members of this committee are independent and include persons representing patients'interests. If it is not possible to involve such an independent local representative in the evaluation, then no clinical trial should be implemented in the country.

2.9 EVALUATION

In the evaluation of a research protocol, special attention should be paid to the following issues:

- the relevance of the research to be carried out in a developing country. Specific attention should be paid when the objective of the clinical trial does not comply with health priorities of the host country;
- the risk/benefit ratio at the individual level, as well as at the community level;
- the impact of the project after its completion. The expected benefits for the local community where the trial takes place should be specified, particularly regarding future access to the potential new treatment, technology transfer and capacity building;
- the involvement of the community at various steps of the process (definition of objectives, elaboration of protocol and of consent modalities, etc…)

The Group notes that wherever research is carried out, the conditions of financing a project and the recompense of the professionals involved in clinical trials should be transparent in order to avoid undue pressure or risk of biais.

2.10 PLACEBO

The use of placebos should be regulated in developing countries in principle by the same rules as in European countries. Any exception must be justified: an obvious one is when the primary goal of the clinical trial is to try to simplify or to decrease the costs of treatment for countries where the standard treatment is not available for logistic reasons or inaccessible because of the cost. It may thus be justified to derogate from the rule of best proven treatment. The justification of using a placebo must be clearly demonstrated in the research protocol submitted to the ethical committees and especially approved by the local committee.
Nevertheless, two members of the Group consider that the use of a placebo for the purpose of developing low cost treatment could mean accepting a "double standard" for poor and rich countries. Thus research in developing countries could lead to a vicious circle: on the one hand, clinical trials in developing countries contribute to developing new treatments which can be patented in rich countries and are then unaffordable for poor countries, and on the other hand the non-availability of treatment in the poorest countries is due partly to the patent costs.

2.11 PROTECTION OF PATIENTS

The standards of insurance, liability and indemnity insurance for the participants in a clinical trial and their families must provide the same kind of protection wherever a trial takes place.

2.12 SUPPLY OF TREATMENT DURING THE TRIALS

In industrialised countries, the reference treatment used in a clinical trial may be provided by the health care services, while the new drug being tested is provided by the sponsor. When a trial is implemented in a country or a community where patients cannot benefit from the standard treatment because of the cost, it is then up to the sponsor to provide it.

2.13 SUPPLY OF TREATMENT AFTER THE END OF THE TRIAL

In industrialised countries, free supply of a proven beneficial new drug to all the participants of a trial after the trial is ended is the rule as long as it is not yet available through the normal health care system. In developing countries, the same rule must be applicable even if this implies supplying the drug for a lifetime if necessary. Moreover, there should be an obligation that the clinical trial benefits the community that contributed to the development of the drug. This can be e.g. to guarantee a supply of the drug at an affordable price for the community or under the form of capacity building. The protocol of clinical trials must specify who will benefit, how and for how long. In order to avoid limitations due to patent rights when the research is carried out mainly with public funding, the results produced should be regarded as falling within the public domain, or else a system of compulsory licences for applications in developing countries should be considered, as already stressed by the Group in its previous opinion n° 16[2].

[2] Opinion on the ethical aspects of patenting inventions involving human stem cells published on 7th May 2002, point 2.9: "*The EGE stresses the fact that it is the responsibility of the states to establish legal procedure for the delivery of complulsory licence and to examine if fair access to health care justifies such a procedure.*"

2.14 INFORMATION OF RESULTS

Scientists, doctors and participants involved in a clinical trial should be informed of the results of the trial. Negative results also must be published and made accessible. More generally, the new knowledge acquired by a research project in a developing country must be made efficiently accessible to the scientific community and to the general population of the country where the research took place. The role played by local scientists and clinicians should be adequately recognized in publications and patents.

2.15 CONCLUSION

The funding of research devoted to solving health problems that are specifically acute in developing countries has a value in itself in terms of solidarity. The Group welcomes the EU policy of funding research in developing countries to fight against poverty-linked diseases.